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Chronic Urticaria

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Abstract Chronic urticaria is defined as case of spontaneous wheals and/or angioedema persisting for a period of at least six weeks. The disease has an average duration of three to five years and is strongly associated with a decrease of quality of life and performance. Current international guidelines recommend the use of non-sedating antihistamines as the first choice in therapy and up-dosing these up to fourfold in cases of non-response. Alternative treatments for the afflicted who do not respond to antihistamine-treatment are also available but are not approved for use on urticaria.

Keywords Urticaria · Chronic urticaria · Wheal · Angioedema · Antihistamine · Omalizumab · Diagnosis · Classification · Treatment

Introduction

In recent years many new findings have underlined the heterogeneity of different subtypes of urticaria. Chronic urticaria is defined as the spontaneous appearance of wheals persisting at least six weeks. This paper is based on the current international guidelines (EAACI/GA^{2}LEN/EDF/WAO guidelines on classification and diagnosis of urticaria and on management of urticaria [1, 2]. In addition recent findings and studies are described and discussed.

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Definition and Classification

Urticaria is a disease entity characterized by the rapid appearance of wheals (Fig. 1) and/or angioedema. Wheal are typically fleeting and last one hour to a maximum 24 hours. They are known to cause itching and sometimes burning. Angioedema is defined as a sudden pronounced swelling of the lower dermis and subcutis. Angioedema can be rather painful and, in contrast to wheals, is less itchy and remains up to 72 hours. Chronic urticaria can present itself with the daily appearance of wheals and/or angioedema but also can cause relapses or an intermittent course of urticaria and/or angioedema occurring at intervals of several days or even weeks. In patients where only angioedema is present, this is grouped as chronic urticaria only if other forms of angioedema (e.g. hereditary angioedema) have been excluded.

Table 1 presents a classification of the clinical use of the different subtypes of urticaria. It is important to note that in patients with chronic urticaria frequently other subtypes can occur, most frequently dermographic urticaria and that these different subtypes need to be addressed possibly in different ways.

An important aspect in the approach to chronic urticaria is monitoring the disease activity, since it helps one to better evaluate treatment success and the impact of the disease on patients. For this purpose a unified scoring system has been introduced. In this simple system, the patient rates the intensity of wheals or pruritus from mild (1) to intense (3). Disease activity is frequently most intense in the evening or at night and, thus, unlike in other more static diseases like psoriasis, doctor evaluations are not as helpful. The scoring system is shown in Table 2.

In addition focused measures on quality of life of urticaria patients have been validated showing that chronic

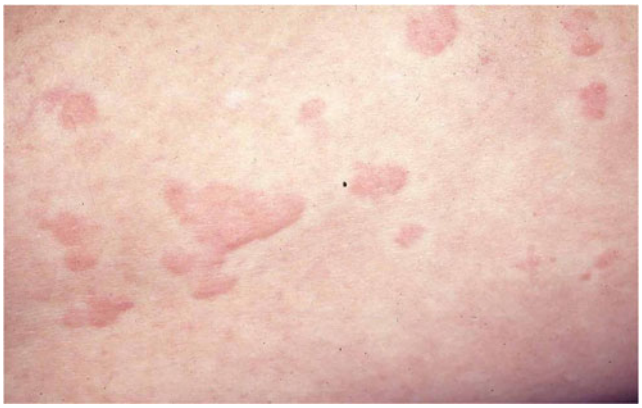


Fig. 1 Wheals

urticaria has a significant impact on the quality of life of urticaria sufferers as well as their performance in learning, education, training and work [3]. This measurement is also valuable in daily practice, since it helps patients themselves to better understand where their specific needs in the treatment are. It is often surprising for a physician to find out that the physical appearance has a higher impact for patients than the itching itself.

Table 1 Classification of urticaria subtypes (presenting with wheals and/or angioedema)

Types	Subtypes	Definition
Spontaneous urticaria	Acute spontaneous urticaria	Spontaneous wheals and/or angioedema <6 weeks
	Chronic spontaneous urticaria	Spontaneous wheals and/or angioedema >6 weeks
Physical urticaria	Cold contact urticaria	Eliciting factor: cold objects/air/fluids/wind
	Delayed pressure urticaria	Eliciting factor: vertical pressure (wheals arising with a 3–12 h latency)
	Heat contact urticaria	Eliciting factor: localized heat
	Solar urticaria	Eliciting factor: UV and/or visible light
	Urticaria factitia/ dermographic urticaria	Eliciting factor: mechanical shearing forces (wheals arising after 1–5 min)
	Vibratory urticaria/ angioedema	Eliciting factor: vibratory forces, e.g. pneumatic hammer
Other urticaria types	Aquagenic urticaria	Eliciting factor: water
	Cholinergic urticaria	Elicitation by increase of body core temperature due to physical exercises, spicy food
	Contact urticaria	Elicitation by contact with urticariogenic substance
	Exercise induced anaphylaxis/ urticaria	Eliciting factor: physical exercise

(*Adapted from* Zuberbier et al. [1])

Table 2 Assessment of disease activity in urticaria patients

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20–50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score: 0–6

Prevalence and Pathophysiological Factors

The prevalence of chronic urticaria is estimated at 1 % of the population, but there is still a lack of larger-section studies in different countries [4].

Regarding pathophysiology, various studies have now shown that infections, autoreactive mechanisms and pseudo-allergic reactions from drugs and food are the most important eliciting factors of chronic urticaria. However a subset of patients, depending on the depth of diagnostic procedures, remains idiopathic.

Regarding infections the most studied infection is helicobacter pylori and an association with chronic urticaria has now been confirmed by several studies and a meta-analysis [1]. Other bacterial infections, such as nasopharynx, or dental infections can also trigger urticaria. The role of viral infections, e.g. hepatitis A and B and that of parasites depends largely on the population. In Europe and North America, for example, these factors do not play a major role. The same holds true for intestinal candidiasis, which has been mentioned in older textbooks, but recent findings failed to support a significant role.

Apart from causing chronic urticaria, infections, especially acute viral infections of the upper respiratory tract, can exacerbate an existing case of chronic urticaria. In addition to infections, non-infectious chronic inflammatory processes have been shown to cause urticaria in a low number of patients, particularly those suffering from reflux esophagitis or, in rare cases, other auto-immune disorders such as systemic lupus erythematosus.

Autoreactive reactions in urticaria were first described as thyroid autoantibodies associated in some patients with chronic urticaria and later by the detection of anti Fc epsilon RI autoantibodies. More recently additional autoreactive reactions have been observed, and the autologous serum test is a screening tool. Pseudo-allergic reactions to drugs are mainly caused by NSAIDs. Aspirin, in particular, needs to be evaluated in such reactions. Due to aspirin's permanent binding to thrombocytes, patients who take as little as a

tablet a week may experience symptoms. Thus, aspirin use needs to be considered in a patient's history. In the past, pseudo-allergic reactions to food were thought to be primarily from preservatives and color additives. It is now known that naturally occurring food ingredients, mainly aromatic compounds such as those found in fresh tomatoes, spices or wine can also frequently cause chronic urticaria. A pseudo-allergen-low diet has been shown to be helpful in 30-60 % of urticaria sufferers, according to the study. Nevertheless, approximately 50 % do not show a total clearance of symptoms but only a reduction of symptom severity. An effective pseudo-allergen-low diet, which needs to be maintained for diagnostic purposes for a period of 3–4 weeks, has now been translated into different languages and has been validated not only in Germany but also in Italy and Turkey [5–7]. The diet as well as supplementary material can be downloaded at http://www.ecarf.org/fileadmin/documents/PAAD_english_050412.pdf

Diagnosis of Chronic Urticaria

The guidelines clearly demonstrate that costly general screening programmes for chronic urticaria are not recommended, since they are not very cost efficient.

Diagnosis should comprise both patient history and physical examination and make use of basic laboratory tests to exclude a severe systemic disease. All additional investigations should be carried out in an individual analysis of the likelihood of the relevance of these factors.

Since patient history is of primary importance in the diagnosis of chronic urticaria, it is useful to use a standardized questionnaire. Items which need to be assessed include the following:

- Time of onset of disease
- Frequency and duration of wheals
- Diurnal variation
- Shape, size, and distribution of wheals
- Associated angioedema
- Associated subjective symptoms of lesion, e.g. itchiness, pain
- Family history regarding urticaria, atopy
- Previous or current allergies, infections, internal diseases, or other possible causes
- Induction by physical agents or exercise
- Use of drugs (NSAIDs, injections, immunizations, hormones, laxatives, suppositories, ear and eye drops, and alternative remedies)
- Food
- Smoking habits
- Type of work
- Hobbies
- Occurrence in relation to weekends, holidays, and foreign travel
- Surgical implantations
- Reactions to insect stings
- Relationship to the menstrual cycle
- Response to therapy
- Stress
- Quality of life related to urticaria

In the following physical examination it is important to exclude possible co-existing physical subtypes of urticaria. The general workup is summarized in Table 3.

Therapy for Urticaria

The ideal therapy for urticaria consists of the identification and, of course, elimination of possible eliciting factors or at least in reducing these factors. However, since this is not always possible, it is very important to address the patient's needs in the beginning, and assure the patient of the excellent possibilities of management with available drugs.

For this purpose the guidelines propose a four-step-algorithm (Fig. 2).

The different principles have been discussed intensely. They are based on evidence and ranked according to the GRADE system. This allows a clear comparison of risk and benefit of different interventions and accordingly a ranking of the steps of the procedures.

In first line treatment with non-sedating second-generation antihistamines is strongly recommended. These drugs do not only have a long standing safety record but have been shown to be effective in a multitude of randomized placebo-controlled clinical trials. However the guidelines emphasize the recommendation to avoid first-generation antihistamines. These older drugs are efficient in controlling urticaria symptoms but they are not more efficient than the modern non-sedating anti-histamines and side effects are unavoidable. While previously recommendations have mentioned the use of sedating antihistamines at night, it has now been discovered that the initiation of sleep is less beneficial than one can achieve with modern sleeping drugs like Zolpidem, as older sedating antihistamines impair REM and frequently cause a hangover the next day, resulting in a reduced reaction capacity and prolonged response of reflexes. This can impair daily activities, such as driving. Thus use of first-generation sedating antihistamines is strongly discouraged. When sedation is desired by patients, experts recommend combining modern non-sedating antihistamines with drugs like Zolpidem, which do not interfere with the sleeping phases. However in most cases, as soon as the itchiness is under control, normal sleeping patterns are easily reached again by patients.

Table 3 Recommended diagnostic tests in frequent urticaria subtypes

Types	Subtypes	Routine diagnostic tests (recommended)	For identification of eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None **
	Chronic spontaneous urticaria	Differential blood count and ESR or CRP omission of suspected drugs (e.g. NSAID)	Test for (i) infectious diseases (e.g. Helicobacter pylon); (ii) type I allergy; (iii) functional autoantibodies; (iv) thyroid hormones and autoantibodies; (v) skin tests including physical tests; (vi) pseudoallergen-free diet for 3 weeks and tryptase***, (vii) autologous serum skin test, lesional skin biopsy
Physical urticaria	Cold contact urticaria	Cold provocation and threshold test (ice cube, cold water, cold wind)	Differential blood count and ESR/CRP cryoproteins rule out other diseases, especially infections
	Delayed pressure urticaria	Pressure test (0.2-1.5 kg/ cm2 for 10 and 20 min)	None
	Heat Contact urticaria	Heat provocation and threshold test (warm water)	None
	Solar urticaria	UV and visible light of different wave lengths	Rule out other light-induced dermatoses
	Dermographic urticaria/ urticaria factitia	Elicit dermographism	Differential blood count, ESR/CRP
Other types of urticaria	Aquagenic urticaria	Wet cloths at body temperature applied for 20 min	None
	Cholinergic urticaria	Exercise and hot bath provocation	None
	Contact urticaria	Prick / patch test read after 20 min	None
	Exercise-induced anaphylaxis/ urticaria	According to history exercise test with/without food but not after a hot bath	None

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NSAID, nonsteroidal anti-inflammatory drugs

* Depending on suspected cause

** Unless strongly suggested by patient history, e.g. allergy

*** As indication of severe systemic disease

Adapted from Zuberbier et al. [1]

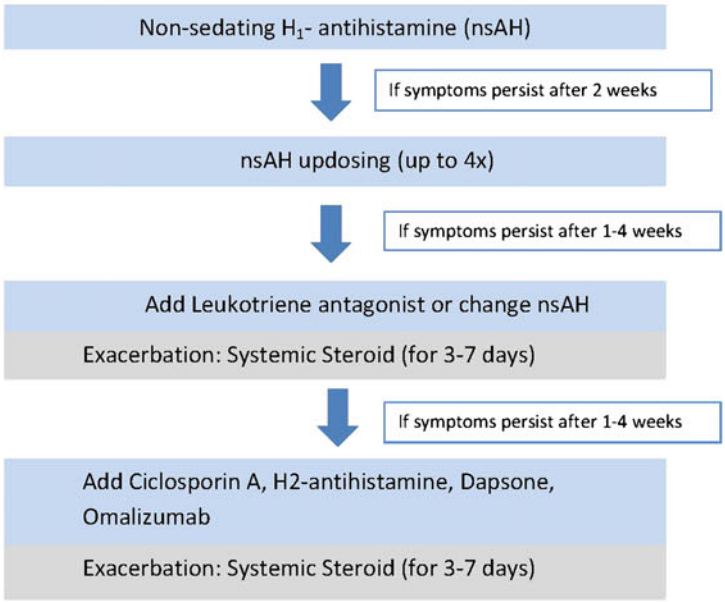
The second level of therapy encompasses increasing the dosage of modern non-sedating second-generation antihistamines. The guidelines are very clear on this issue, stating that this mode of action offers the best risk–benefit outcome, in comparison to alternative treatments. Several studies have proven that there is a dose-dependent effect of modern non-sedating antihistamines and that up-dosing up to the quadruple dose is safe measure (for overview see [8]). This may be due to the non-histamine-receptor-mediated effects of this class of drugs.

In principle when up-dosing, one needs to remember that this treatment is off-label (as are all other alternative options in urticaria), and that patients need to be advised of this circumstance. In choosing the antihistamine for up-dosing, one must take care that some of the modern second-generation antihistamines have a dose-dependent effect of sedation in higher dosages, and patients need to be advised of this. Furthermore some antihistamines may also show drug-interactions. The safest for updosing are metabolites e.g. bilastine, cetirizine, desloratadine, fexofenadine [9].

The third level of treatment was widely discussed during the guideline preparation, which considers that the majority of well-documented effective alternative treatments like cyclosporin A are expensive and can cause severe side effects. Thus alternatives should be explored before going to level IV treatment.

Therefore, the guidelines recommend changing the non-sedating antihistamine used in level II or adding antileukotriens as well as a short course of corticosteroids for not more than three days. The reasoning behind this is not so much based on evidence but on individual reports leading to the assumption that a group of patients might respond to these actions. However if this is not beneficial, patients should not be kept too long on non-effective treatment since a major aim of the guidelines is to offer complete symptom-control for patients.

Recommended treatment algorithm for chronic urticaria



Comments on procedure on algorithm for chronic urticaria

First level: High quality evidence

- Low cost (worldwide availability also in developing countries mostly cheaper than old sedating Antihistamines)
- Very good safety profile
- Very good evidence for efficacy

Second Level: Low quality evidence

- Low cost
- Good safety profile
- Good evidence for efficacy

Third Level: Very low quality evidence

- Low -to medium-low cost
- Good safety profile
- Insufficient or no evidence for efficacy in high quality RCT

Fourth Level:

- Ciclosporin A:
  - Medium to high cost
  - Moderate safety profile
  - Moderate level of evidence for efficacy
- H2-Antihistamine:
  - Low cost
  - Medium level of side effects
  - Low level of evidence for efficacy
- Dapsone:
  - Low cost
  - Medium level of side effects
  - Low level of evidence for efficacy
- Omalizumab
  - High cost
  - Good safety profile
  - Low level of evidence for good efficacy

Fig. 2 Recommended treatment algorithm for chronic urticaria. (*Adapted from* Zuberbier et al. [2])

In level IV, four different treatment options are recommended; however, many other possibilities for treating chronic urticaria have been reported in small studies or case reports. They are not part of the recommended practices in the guidelines but might be of interest in case where level IV interventions fail. These are all listed in the guidelines (http://www.ga2len.net/).

Regarding the four options in level IV, H2 antihistamines in combination with H1 antihistamines had the least amount of research support. According to the GRADE system, this treatment option is listed since the cost and potential side effects speak in its favor. The next best data exists for additional treatment of the dapsone and cyclosporin A. However the most effective drug in level IV-treatment is Omalizumab. In double-blind placebo-controlled studies, this drug achieved a response rate of more than 70 % complete symptom-resolution in patients who were refractory to antihistamine-treatment. This high rate of efficacy has not been reached by any other drug in urticaria treatment so far. The mode of action for this anti-IgE-treatment is, however, not clear at present, since unlike in asthma, the treatment does not need to be adjusted according to total IgE-levels.

In treating urticaria, it must be noted that disease activity should be constantly monitored and a step-down procedure should be evaluated at regular intervals. After three months of complete response, treatment intensity can likely be reduced.

Conclusions

Chronic urticaria is a challenging disease for the patient and the physician. Nevertheless, the latest research has brought new insight into the pathophysiology and possible eliciting factors of the disease. Most importantly, though, studies have given us new tools in the treatment of chronic urticaria. With modern antihistamines and new developments like Omalizumab for treating resistant urticarial, patients can be reassured that this formerly extremely difficult to manage disease is now under better control.

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